

## WHAT IS CLAIMED

1. A method of making a chimeric mouse, comprising:  
 a. creating an immunetolerant mouse which has  
 a degenerated liver; and  
 b. transplanting xenogenic mammalian  
 hepatocytes capable of being infected with at least one  
 compatible mammalian hepatitis virus to repopulate the  
 parenchyma of the degenerated liver.

2. The method of claim 1, which comprises infecting  
 the xenogenic mammalian hepatocytes with hepatitis virus prior  
 to said transplanting.

3. The method of claim 1, which comprises infecting  
 the xenogenic mammalian hepatocytes with hepatitis virus  
 following said repopulation.

4. The method of claim 1, which comprises selecting  
 the xenogenic mammalian hepatocytes from the group consisting  
 of human, chimpanzee, baboon, wooly monkey, ground squirrel,  
 and woodchuck hepatocytes.

5. The method of claim 1, wherein the compatible  
 mammalian hepatitis virus is at least one of a compatible  
 mammalian hepatitis A virus, hepatitis C virus, hepatitis D  
 virus coinfecting with hepadnavirus, hepatitis E virus,  
 hepatitis F virus or hepadnavirus.

6. The method of claim 1, wherein the  
 immunetolerant mouse which has a degenerated liver is created  
 by:

a. crossing a hemizygous or homozygous  
 urokinase-type plasminogen activator (uPA) transgenic mouse  
 with a homozygous Recombination Activation Gene 2 (RAG-2)

- 7 knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous  
 8 sibling mice; and  
 9 b. crossing the F1 mouse to another sibling F1  
 10 mouse or to a RAG2 homozygous mouse to generate a uPA  
 11 hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

7. The method of claim 6, wherein the xenogenic mammalian hepatocyte is from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

8. ~~A chimeric mouse model system for hepatitis comprising an immunetolerant mouse having a degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes that are capable of being infected with a compatible mammalian hepatitis virus.~~

9. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

10. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

11. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes is a member selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

12. The chimeric mouse model system of claim 8, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfectd with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Sub F2 13. The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and is homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

Sub C3 14. The chimeric mouse model system of claim 13, wherein the xenogenic mammalian hepatocyte is derived from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

1 15. A method for screening a test compound for anti-viral activity, comprising:

- 2 a. administering said test compound to an  
3 immunetolerant chimeric mouse which has a degenerated liver  
4 parenchyma repopulated with transplanted xenogenic mammalian  
5 hepatocytes and wherein the xenogenic mammalian hepatocytes are  
6 infected with at least one compatible mammalian virus; and  
7 b. assaying the level of replication of the  
8 virus.  
9

16. The method of claim 15, wherein the mammalian virus is at least one hepatitis virus.

17. The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

18. The method of claim 15, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus prior to said transplanting.

19. The method of claim 16, which comprises infecting the xenogenic mammalian hepatocytes with the

compatible mammalian virus following said repopulating step.

20. The method of claim 15, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

21. The method of claim 15, wherein the compatible mammalian virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfecting with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

22. The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

Sub C<sup>4</sup> 23. ~~The method of claim 22, wherein the xenogenic mammalian hepatocyte is derived from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).~~

24. The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Sub D<sup>4</sup> 25. A method for screening a test compound for anti-cancer activity, comprising:  
 a. administering said test compound to an immunetolerant chimeric mouse which has degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes and wherein the xenogenic mammalian hepatocytes are

7 infected with at least one compatible mammalian hepatitis  
8 virus; and

9 b. assaying the mice for the development of  
10 hepatocellular carcinoma in said mice.

26. The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

27. The method of claim 25, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

28. The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

29. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with a hepatitis virus prior to said transplantation step.

30. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting step.

31. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulating step.

32. The method of claim 25, which comprises

selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

33. The method of claim 25, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfecting with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

*8/16/6* 34. The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

*Sub C<sup>6</sup>* 35. The method of claim 33, wherein the xenogenic mammalian hepatocyte is derived from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

36. The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

*add C<sup>7</sup>*

*add D<sup>6</sup>*

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